IJPSR (2013), Vol. 4, Issue 7 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 07 March, 2013; received in revised form, 08 May, 2013; accepted, 17 June, 2013

IMPLICATION OF NANOPARTICLES FOR CONTROLLED DRUG DELIVERY SYSTEM

Dipti Desai*[1] and Dushyant Shah [2]

Department of Pharmacy, Pioneer Pharmacy Degree College [1], Syajipura, Nr. Aajwa cross road, Vadodara, Gujarat, India

Department of Pharmacy, APMC College of Pharmaceutical Education & Research [2], Himatnagar, Gujarat, India

Keywords:

Nanoparticles, Biodegradable polymer, Controlled drug release

Correspondence to Author:

Dipti Desai

Department of Pharmacy, Pioneer Pharmacy Degree College , Syajipura, Nr. Aajwa cross road, Vadodara, Gujarat, India

E-mail: diptidesai2001@yahoo.com

ABSTRACT: Pharmaceutical nanoparticles are submicron-sized, colloidal vehicles that carry drugs to the target or release drugs in a controlled way in the body. Controlled drug delivery offers advantages like reduced dosing frequency, better therapeutic control, reduced side effects, and, consequently, better patient compliance. Biodegradable polymers are utilized to prepare Nanoparticles which offers advantages like versatile degradation kinetics, non-toxicity, and biocompatibility. Nanoparticles can be prepared by various techniques & are evaluated for parameters like: Particle size, Morphological properties, Thermal properties, surface chemistry & drug release etc. Nanoparticles can be converted into dry form & formulated in various dosage forms depending on the route of application. Several marketed formulation based on controlled drug delivery are also available which is the fruitful result of the development of biodegradable polymer, newer techniques for preparation, scale up procedure & better control over all the required manufacturing processes.

INTRODUCTION: Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm; where the drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix [1].

Controlled drug delivery system attributes to release of drug from dosage form in a controlled manner which can have benefits like maintenance of drug concentration in systemic circulation without any more fluctuation, reduced dose & dosing frequency & hence, reduced side effects and improved patient compliance [2-4].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.4(7).2478-88

Article can be accessed online on: www.ijpsr.com

Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed [5].

The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen. This system also helps to increase the stability of drugs/proteins and possess useful controlled release properties.

After preparation, nanoparticles are usually dispersed in liquid.

Such a system can be administered to humans for example by injection, by the oral route, or used in ointments and ocular products. Alternatively, nanoparticles can be dried to a powder, which allows pulmonary delivery or further processing to tablets or capsules also.

Types of Nanoparticles [6, 7]**:**

1. **Carbon Nanotube**: They are hollow cylinders made of carbon atoms. They can also be filled & sealed, forming test tubes or potential drug delivery devices.

2. **Nanoshells**: Nanoshells are hollow silica spheres covered with gold. Antibodies can be attached to their surfaces, enabling the shells to target certain shells such as cancer cells. They can also be filled with drug containing polymer.

3. **Dendrimers**: Dendrimers are highly branched structures gaining wide use in nanomedicine because of the multiple molecular "hooks" on their surfaces that can be used to attach cell-identification tags, fluorescent dyes, enzymes and other molecules.

4. **Quantum dots**: Quantum dots are nanosized semiconductors that, depending on their size, can emit light in all colors of the rainbow. These nanostructures confine conduction band electrons, valence band holes, or exactions in all three spatial directions. Examples of quantum dots are semiconductor nanocrystals and core-shell nanocrystals, where there is an interface between different semiconductor materials. They have been applied in biotechnology for cell labeling and imaging, particularly in cancer imaging studies.

5. **Superparamagnetic nanoparticles**: Superpara magnetic molecules are those that are attracted to a magnetic field but do not retain residual magnetism after the field is removed. Nanoparticles of iron oxide with diameters in the 5-100 nm range have been used for selective magnetic bioseparations.

6. **Nanorods**: Typically 1-100 nm in length, nanorods are most often made from semiconducting materials and used in nanomedicine as imaging and contrast agents. Nanorods can be made by generating small cylinders of silicon, gold or inorganic phosphate, among other materials.

7. **Solid lipid nanoparticles**: Solid Lipid Nanoparticles consist of a solid lipid matrix, where the drug is normally incorporated, with an average diameter below 1 μm. They can be used for brain targeting.

8. **Polymeric nanoparticles**: Polymeric nano-particles (PNPs) consist of a biodegradable polymer. Biocompatibility is an essential feature for potential application as tissue engineering, drug and gene delivery and new vaccination strategies.

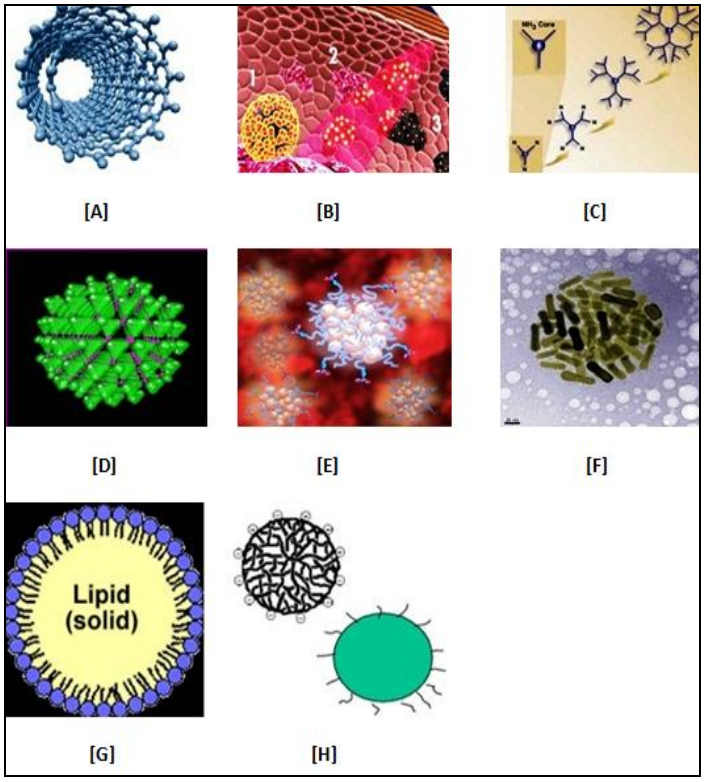

FIG.1 (A)FULLERENES: BUCKYBALLS AND CARBON TUBE; (B) NANOSHELLS; (C) DENDRIMERS; (D) QUANTUM DOTS; (E) SUPERPARAMAGNETIC NANOPARTICLES; (F) NANORODS; (G) SOLID LIPID NANOPARTICLES; (H) POLYMERIC NANO-PARTICLES

Controlled Drug Delivery: Controlled drug delivery system prolong the drug release, delivers the drug at predetermined rate, locally or systemically for specified period of time. Controlled release of drugs can maintain the drug in the desired therapeutic range for days, weeks, months, and for some products, even years.

Compared to conventional oral dosage forms, they offer several advantages including [8]:

1. Controlled administration of a therapeutic dose at a desirable rate of delivery.
2. Maintenance of drug concentration within an optimal therapeutic range for prolonged period of time.
3. Maximization of efficacy-dose relationship.
4. Reduction of adverse side effects.
5. Minimization of the needs for frequent dose intake.
6. Enhancement of patient compliance

In order to achieve efficient disease management, the concentration of released drugs from polymeric matrices should be within the therapeutic window with minimal fluctuation in blood levels over prolonged periods of time at the intended site of action The release of drug can be controlled by diffusion, erosion, osmotic-mediated events or combinations of these mechanisms.

Typically, a triphasic release pattern is observed, consisting of an initial burst [9], primarily attributed to drug precipitates at the particle surface and surface pores in the polymer, and the osmotic forces in highly water-soluble peptide formulations [11], a lag period depending on the molecular weight and polymer end-capping [10] and finally erosion-accelerated release [11].

Considering release rate control as a key parameter, a decrease in particle size (i.e., an increase in the specific surface area) results in higher release [11]. Also, higher porosity of the particles inducing a larger inner surface can increase the influx of the release medium into the particles and, thereby, facilitate the drug diffusion rate [12]. In addition, the specific properties of the polymer matrix (e.g., the chain length, flexibility and swelling behavior, potential interactions between polymer and drug) will significantly influence the drug release rate [13, 14]. Therefore, switching to a different molecular weight or an end group capped polymer, and the use of block copolymers will alter the diffusion and drug release rate [15, 16].

To achieve zero-order release kinetics indicative of uniform release with respect to time, which is desired for most applications, a combination of fast- and slow-releasing particles or the use of copolymers are possible alternative advanced methods [17, 18]. A one-time only dose can be achieved by co-injection of a bolus of soluble drug as a loading dose and zero-order releasing microspheres as a maintenance dose.

The development of polymeric controlled release system introduced a new concept in drug administration. They are an attractive alternative for progressive and long-term delivery of therapeutic agents.

The therapeutic agents are well protected in these polymeric dosage forms offering the advantage of delivering the drugs to tissues in sustained fashion avoiding repeated drug administration. These also provide the opportunity to achieve site-specific delivery. Because macromolecules, such as peptides and proteins, are very sensitive in terms of stability, their encapsulation allows protection, especially against gastrointestinal enzymes and pH effects, when administered per orally.

Polymeric release systems can be classified into reservoir and matrix systems.

1. **A Matrix-type system**: Drug is dispersed homogeneously throughout polymeric matrix and

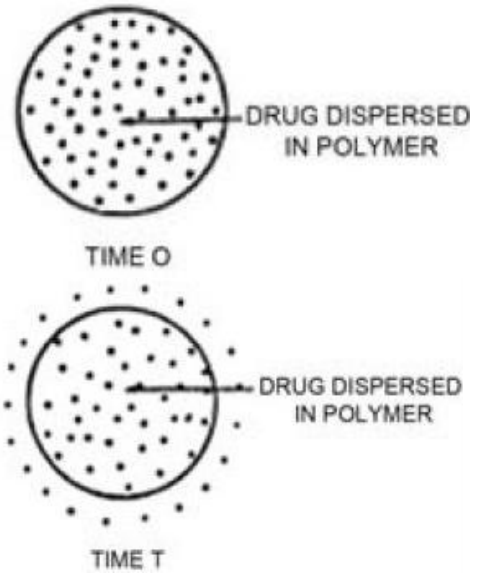

FIG. 2: DRUG RELEASE FROM MATRIX SYSTEM

2. **A Reservoir type system**: Drug is surrounded by a polymer wall.

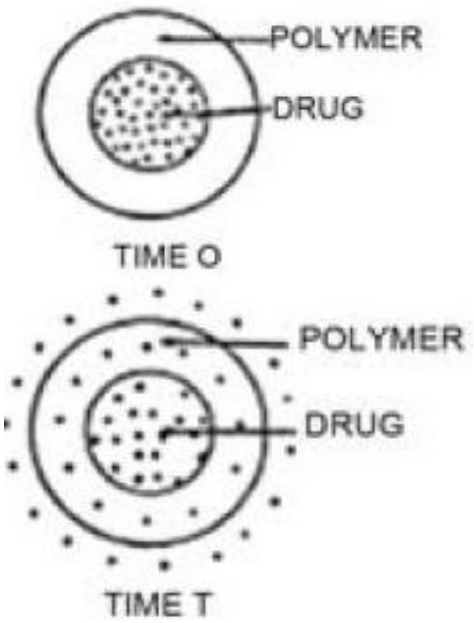

FIG. 3: DRUG RELEASE FROM RESERVOIR SYSTEM

Mechanisms of Drug Release: The polymeric drug carriers deliver the drug at the tissue site by any one of the three general physico-chemical mechanisms.

1. By the swelling of the polymer nanoparticles by hydration followed by release through diffusion.

2. By an enzymatic reaction resulting in rupture or cleavage or degradation of the polymer at site of delivery, there by releasing the drug from the entrapped inner core.

3. Dissociation of the drug from the polymer and its de-adsorption/release from the swelled nanoparticles.

Polymers used in preparation of Nanoparticles: The polymers should be compatible with the body in the terms of adaptability (non-toxicity) and (non-antigenicity) and should be biodegradable and biocompatible. Polymeric inactive ingredients for FDA-approved drug products [2, 19].

Natural: Starch, Hyaluronate, Human albumin, Gelatin, Alginic acid, Collagenl.

Polyester-based synthetic polymers: PLGA, Poloxamer, Polyvinyl pyrrolidone, Ethyl cellulose, Sodium pyrrolidone carboxylate, Povidone, PLA, PEG, PVA, KOLLIDON VA 64

Nanoparticles for Controlled Release Delivery: The area of nanoparticle drug delivery is gaining much attention in recent years for a variety of administration routes, including pulmonary nanomedicine delivery. To improve the bioavailability of PLGA nanoparticles, Barichello *et al.*, formulated surface bound peptides using nanoprecipitation solvent displacement method. Insulin was preferentially surface bound on the PLGA nanoparticles and the amount of insulin encapsulated into nanoparticles was related to composition and pH of the buffer solution; the optimal pH was close to the isoelectric point of insulin.

Insulin-loaded PLGA nanoparticles were prepared by w/o/w and s/o/w encapsulation methods with a stabilizer, Pluronic F68. Comparing the nanoparticles prepared by s/o/w method, the insulin release rate was higher for the batches prepared by w/o/w method containing stabilizers.

Also the presence of stabilizers resulted in a sustained release of insulin, therefore a prolonged reduction of blood glucose level in diabetic rats [20].

Magnetically modulated nanoparticles are used for developing in vivo imaging and delivering drugs to targeted sites, such as tumors. Non-targeted applications of magnetic nanospheres include their use as contrast agents (MRI) and as drug carriers that can be activated by a magnet applied outside the body. In another study, this magnetic force was used to improve the efficiency of orally delivered protein therapeutics.

When the external magnetic field was applied to the intestine, the transit time of magnetic particles slowed down; therefore, the residence time of the orally delivered particles in small intestine is extended and absorption of protein increases [21].

TABLE 1: THE LIST OF MARKETED CONTROLLED RELEASE POLYMERIC PHARMACEUTICAL PRODUCTS AND CLINICAL TRIALS [22]

PRODUCT NAME	DRUG & POLYMER	COMPANY	INDICATION
Arestin®	Minocycline/ PLGA	OraPharma	Periodontitis, powder administered into periodontal pocket
Decapeptyl® Depot	Triptorelin/ PLGA	Ferring	Prostate cancer, Edometriosis, i.m.
Decapeptyl® SR	Triptorelin/PLA, PLGA	Ipsen	Prostate cancer, Endometriosis, i.m.
Lupron Depot®	Leuprolide/PLA, PLGA	TAP	Prostate cancer, Endometriosis, i.m.
Nutropin®	Human growth hormone/ PLGA	Genetech	Treatment of growth failure, s.c.
Sandostatin® LAR	Octreotide/ PLGA- Glucose	Novartis	Acromegaly, i.m.
Somatuline® PR	Lanreotide/ PLGA	Ipsen	Acromegaly, i.m.
Suprecur® MP	Buserelin/ PLGA	Sanofi-Aventis	Endometriosis, i.m.
Vivitrol®	Naltrexon/ PLGA	Alkernes	Alcohol depence treatment, i.m.
Trelstal™ LA Depot	Triptorelin/ PLA	Prostate cancer	Pfizer, i.m.
Risperdal® Consta™	Risperidone/ PLGA	Janssen-Cilag	Schizophrenia, i.m.

i.m. = intramuscularly injected; s.c. = subcutaneously injected

Techniques of preparation of Nanoparticles [23]:

A. Nanoparticles prepared by Polymerization process [24]:

Polymerization method: In this method, monomers are polymerized to form nanoparticles in an aqueous solution. Drug is incorporated either by being dissolved in the polymerization medium or by adsorption onto the nanoparticles after polymerization completed. The Nanoparticle suspension is then purified to remove various stabilizers and surfactants employed for polymerization by ultracentrifugation and re-suspending the particles in an isotonic surfactant-free medium. This technique has been reported for making polybutylcyanoacrylate or poly (alkylcyanoacrylate) nanoparticles. Nanocapsule formation and their particle size depend on the concentration of the surfactants and stabilizers used.

Decreased miscibility of organic solvents with water is associated with an increase in their resultant interfacial tension and thus increases in size of the nanoparticles. The higher the viscosity of the organic phase, greater will be surface tension and ultimately the particle size of the nanoparticles will be increase. An increase in molecular weight of polymers is associated with a decrease in number of end carboxyl groups and hence lowers the zeta potential of the resulting particles.

Additives present in the formulation may also significantly affect the surface charge. Pluronic F-68, PVA like surfactants may be added to improve steric stability of nanoparticles. Two types of polymerization processes have been adopted to prepare polymeric nanoparticles.

1. **Dispersion Polymerization**: Dispersion polymerization starts with monomer, an initiator, solvent in which the formed polymer is insoluble, and a polymeric stabilizer. Polymer forms in the continuous phase and precipitates into a new particle phase stabilized by the polymeric stabilizer. Small particles are formed by aggregation of growing polymer chains precipitating from the continuous phase as these chins exceed a critical chain length. Coalescence of these precursor particles with themselves and with their aggregates results in the formation of stable colloidal particles, which occurs when sufficient stabilizer covers the particles.

2. **Emulsion Polymerization**: In this technique the monomer is emulsified in non-solvent containing surfactant, which leads to the formation of monomer swollen micelles and stabilized monomer droplets. The polymerization is performed in the presence of initiator. Emulsion polymerization may be performed using either organic or aqueous media as continuous phase.

Poly (methyl methacrylate), poly (alkyl cyanoacrylate), acrylic copolymer, polystyrene, poly (vinyl pyridine) and polyacrolen nanoparticles are prepared by emulsion polymerization technique.

B. **Nanoparticles prepared from Preformed Polymers:** Several techniques have been suggested to prepare the biodegradable polymeric nanoparticles from preformed polymers such as poly (D, L-lactide) (PLA), poly (D, L-glycolide) (PLG) and poly (D, L-lactide-co-glycolide) (PLGA). The basic methodologies of the commonly used preparation methods are as follows:

1. **Emulsion/Evaporation**: This is one of the most frequently used methods. The preformed polymer and drug are first dissolved in a water-immiscible organic solvent, which is then emulsified in an aqueous solution containing stabilizer. The emulsification is brought about by subsequent exposure to a high-energy source such as an ultrasonic device, homogenizer, or colloid mill.

   The organic phase is evaporated under reduced pressure or vacuum, resulting in the formation of the aqueous dispersion of nanoparticles. The nanoparticles are collected by ultracentrifugation and washed with distilled water to remove stabilizer residues or any free drug and lyophilized for storage (Guarrero Q *et al* 1998; Song CX 1997).

   Modification of this method, known as high-pressure emulsification solvent evaporation (HPESE), has been reported by Jaiswal *et al* (2004) This method involves preparation of a coarse emulsion, which is then subjected to homogenization under high-pressure followed by overnight stirring to remove organic solvent. This method has the advantage of obtaining small, monodispersed nanoparticles with high encapsulation efficiency and reproducibility.

   The emulsion evaporation method can be used for preparation of particles with sizes varying from a few nanometers to micrometers by controlling the stirring rates and conditions (Ubrich N2004; Allemann E 1992).

2. **Double emulsion process**: The emulsion evaporation method suffers from the limitation of poor entrapment of hydrophilic drugs because of their diffusion and partitioning from the dispersed oil phase into the aqueous continuous phase. Therefore, to encapsulate hydrophilic drugs and proteins, the double-emulsion technique is employed, which involves the addition of aqueous drug solution to organic polymer solution under vigorous stirring to from a w/o emulsion. This w/o emulsion is added into second aqueous phase containing more stabilizers with stirring to form the w/o/w emulsion.

   The emulsion is then subjected to solvent removal by evaporation (Vandervoort J *et al.*, 2002). A number of hydrophilic drugs like the peptide leuprolide acetate, a lutenizing hormone-releasing agonist, vaccines, proteins/peptides and conventional molecules have been successfully encapsulated by this method. After evaporation of organic solvent under reduced pressure, the polymer precipitates and nanoparticles can be isolated by centrifugation at high speed. The formed nanoparticles must be thoroughly washed before Lyophillization.

3. **Salting-Out:** This technique involves the addition of polymer and drug solution in a slightly water miscible solvent such as acetone to an aqueous solution containing the salting out agent and a colloidal stabilizer under vigorous mechanical stirring. When this o/w emulsion is diluted with a sufficient volume of water, it induces the formation of Nanoparticles by enhancing the diffusion of acetone into the aqueous phase. The remaining solvent and salting-out agent are eliminated by cross-flow filtration (Allemann E 1992).

   Several manufacturing parameters can be varied including stirring rate, internal/external phase ratio, concentration of polymer in the organic phase, type of electrolyte, concentration, and type of stabilizer in the aqueous phase. . By considering the entrapment efficiency of nanoparticles, this method is most suitable for water insoluble drugs. Salt permeate biological systems and are crucial for life.

4. **Emulsification-Diffusion:** This is another widely used method involving polymer solution in partially water miscible solvent (such as ethyl acetate, benzyl alcohol, propylene carbonate) presaturated with water, added to an aqueous solution containing stabilizer under vigorous stirring. The subsequent addition of water to the system destabilizes the equilibrium between the two phases and causes the solvent to diffuse into the external phase, resulting in reduction of the interfacial tension (Takeuchi H *et al*., 2001) and in nanoparticle formation, which gradually becomes poorer in solvent.

   Although this method is a modification of the salting out procedure, it provides the advantage of avoiding the use of salts and thus eliminates the need for intensive purification steps. While this method also suffers from low entrapment efficiency of hydrophilic drugs in nanoparticles, incorporation of medium chain glyceride into aqueous solution has been found to improve the encapsulation efficiency of water-soluble drugs into nanospheres offering the advantage of simplicity, narrow particle size distribution, and ready dispersibility of the resultant particles.

5. **Nanoprecipitation:** In nanoprecipitation, introduced by Fessi and co-workers, the particle formation is based on precipitation and subsequent solidification of the polymer at the interface of a solvent and a non-solvent. Thus, the process is often called solvent displacement or interfacial deposition. This method is usually employed to incorporate lipophilic drugs into the carriers based on the interfacial deposition of a polymer following displacement of a semi-polar solvent miscible with water from a lipophilic solution (Molpeceres J 1996; Barichello J.M. 1999).

   The polymer is dissolved in a water miscible organic solvent (or solvent mixture) and added to an aqueous solution, in which the organic solvent diffuses. Particle formation is spontaneous, because the polymer precipitates in the aqueous environment. According to the current opinion, the Marangoni effect is considered to explain the process [28]: solvent flow, diffusion and surface tensions at the interface of the organic solvent and the aqueous phase cause turbulences, which form small droplets containing the polymer. Subsequently, as the solvent diffuses out from the droplets, the polymer precipitates. Finally, the organic solvent is typically evaporated with the help of a vacuum.

   The injection rate of the organic phase into the aqueous phase affects the particle size. It was observed that a decrease occurs in both particle size and drug entrapment as the rate of mixing of the two phases increase. This method gave relatively narrow particle size distribution for different formulations evaluated.

   The drug loading efficiency was found to be lower for the hydrophilic drugs than lipophilic drugs because of their poor interaction with the polymer leading to diffusion of the drug, from the polymer in the organic phase, to the external aqueous environment, although exceptions were found, as seen in case of proteins and peptides.

   Improved bioavailability of proteins and peptides was demonstrated using PLGA nanoparticles by the nanoprecipitation method (Barichello J.M., 1999). Govender *et al*., (1999) showed improved incorporation of the water-soluble drug, procaine hydrochloride, into PLGA nanoparticles by increasing the aqueous phase pH and replacing procaine hydrochloride by procaine dehydrate base. The difficulty faced in this preparation technique is the choice of drug/polymer/solvent/nonsolvent system in which the nanoparticles would be formed and the drug efficiently entrapped.

Limitation in existing methods: Production of nanoparticles has been limited by the difficulties and complexities of preparation methods. Conventional approaches used to prepare nanoparticles have notable disadvantages, including the relatively high cost of producing these delivery systems; the unknown toxicity of solvents and reagents used to make the delivery systems; the use of rigorous processes such as interfacial polymerization and/or high-torque mechanical mixing, homogenization, or micro fluidization, which may be damaging to biotechnology derived drugs; the inability to easily and reproducibly produce biologically-stable particles; and the low encapsulation efficiency of many types of drugs.

The most commonly used preparation methods require use of organic solvents, which have the tendency to denature protein drugs and other macromolecules. Furthermore, to obtain the particles in the nano size range, a large amount of emulsifiers and high-energy homogenizers to reach high shearing forces are necessary. These high-energy shearing forces can disturb the integrity of the macromolecules. The toxic nature of certain organic solvents requires nanoparticles purification, which adds to cost and time.

Characterization of Nanoparticles [25, 26]: Characterization of the nanoparticle carrier systems to thoroughly understand the properties is essential before putting them to pharmaceutical application. After preparation, nanoparticles are characterized at two levels. The physicochemical characterization consists of the evaluation of the particle size, size distribution, and surface properties (composition, charge, hydrophobicity) of the nanoparticles. The biopharmaceutical characterization includes measurements of drug encapsulation, in vitro drug release rates, and in vivo studies revealing bio-distribution, bioavailability, and efficacy of the drug.

There are many sensitive techniques for characterizing nanoparticles, depending upon the parameter being looked at.

TABLE 2: PARAMETERS FOR CHARACTERIZATION OF NANOPARTICLES

Sr. No.	PARAMETER	TEST
1	Particle size and size distribution	Laser light scattering (LLS)
2	Morphological properties	Photon correlation spectroscopy (PCS) Scanning electron microscopy (SEM), Transmission electron microscopy (TEM)
3	Surface chemistry	Atomic force microscopy (AFM) X-ray photoelectron spectroscopy (XPS) Fourier transform infrared spectroscopy (FTIR)
4	Thermal properties	Nuclear magnetic resonance spectroscopy (NMR) Differential scanning calorimetry (DSC) Differential thermal analysis (DTA) Differential thermo gravimetry (DTG)

Particle size and Zeta potential measurements: Particle size and size distribution are the most important characteristics of nanoparticle systems. They determine the *in vivo* distribution, biological fate, toxicity and the targeting ability of nanoparticle systems. In addition, they can also influence the drug loading, drug release and stability of nanoparticles.

The zeta potential of a nanoparticle is commonly used to characterize the surface charge property of nanoparticles [38]. It reflects the electrical potential of particles and is influenced by the composition of the particle and the medium in which it is dispersed. Nanoparticles with a zeta potential above (+/-) 30 mV have been shown to be stable in suspension, as the surface charge prevents aggregation of the particles.

The zeta potential can also be used to determine whether a charged active material is encapsulated within the center of the nanocapsule or adsorbed onto the surface.

Drug Release: To develop a successful nanoparticulate system, both drug release and polymer biodegradation are important consideration factors. In general, drug release rate depends on:

(1) Solubility of drug;

(2) Desorption of the surface bound/adsorbed drug;

(3) Drug diffusion through the nanoparticle matrix;

(4) Nanoparticle matrix erosion/degradation; and

(5) Combination of erosion/diffusion process. Thus solubility, diffusion and biodegradation of the matrix materials govern the release process.

Various methods which can be used to study the in vitro release of the drug are:

(1) Side-by-side diffusion cells with artificial or biological membranes;

(2) Dialysis bag diffusion technique;

(3) Reverse dialysis bag technique;

(4) Agitation followed by ultracentrifugation/ centrifugation;

(5) Ultra-filtration or centrifugal ultra-filtration techniques.

Usually the release study is carried out by controlled agitation followed by centrifugation. Due to the time-consuming nature and technical difficulties encountered in the separation of nanoparticles from release media, the dialysis technique is generally preferred.

Surface Chemistry Analysis: X-ray photon spectroscopy, Fourier transform infrared spectroscopy, nuclear magnetic spectroscopy are the techniques employed to analyze the surface chemistry.

Currently, the fastest and most routine method of determining particle size is by photon-correlation spectroscopy or dynamic light scattering. Photon-correlation spectroscopy requires the viscosity of the medium to be known and determines the diameter of the particle by Brownian motion and light scattering properties [33]. The results obtained by photon-correlation spectroscopy are usually verified by scanning or transmission electron microscopy (SEM or TEM).

Molecular weight: Polymer molecular weight influences the nanoparticle size, encapsulation efficiency and degradation rate of the polymer, hence affecting the release rate of the therapeutic agent. A low molecular weight polymer can be used to prepare small-sized nanoparticles but at the expense of reduced encapsulation efficiency (Hans M L, Lowman A M, 2002). The average molecular weights and polydispersity of the polymers are found by size exclusion chromatography (Park T J, 1995)

Crystallinity: The physical state of both the drug and the polymer are determined because this will have an influence on the *in vitro* and *in vivo* release characteristics of the drug. The crystalline behavior of polymeric nanoparticles is studied using X-ray diffraction and thermo-analytical methods such as differential scanning calorimetry (Ubrich N. *et al*, 2004) (DSC) and differential thermal analysis (DTA), (Oh I *et al*, 1999) DSC and X-ray diffraction techniques are often combined to get useful information on the structural characteristics of both drugs and polymers.

Application of Nanoparticles [27]:

The advantages of using nanoparticles as a drug delivery system include the following:

1. Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parenteral administration.

2. They control and sustain release of the drug during the transportation and at the site of localization, altering organ distribution of the drug and subsequent clearance of the drug so as to achieve increase in drug therapeutic efficacy and reduction in side effects.

3. Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents. Drug loading is relatively high and drugs can be incorporated into the systems without any chemical reaction; this is an important factor for preserving the drug activity.

4. Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.

5. The system can be used for various routes of administration including oral, nasal, parenteral, intra-ocular etc.

Nanoparticles have versatile potential for efficient exploitation of different drug delivery formulations and routes because of the properties provided by their small size. These possible benefits include controlled release, protection of the active pharmaceutical ingredient and drug targeting.

Nanoparticles are expected to offer new solutions e.g. for gene therapy and delivery of peptide drugs. Generally, nanoparticles are applied as an injectable or oral solution, but their use as dried material in formulations such as tablets or inhalable powders is equally conceivable.

LIMITATIONS:

a) Involves higher manufacturing costs which may in turn lead to increase in the cost of formulation

b) Involves use of harsh toxic solvents in the preparation process

c) May trigger immune response and allergic reactions

d) Extensive use of poly (vinyl alcohol) as stabilizer may have toxicity issues

Their small size and large surface area can lead to particle- particle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms. In addition, small particles size and large surface area readily result in limited drug loading and burst release. These practical problems have to be overcome before nanoparticles can be use clinically or made commercially available.

CONCLUSIONS: Nanoparticles have versatile potential for efficient exploitation of different drug delivery formulations and routes because of the properties provided by their small size. These possible benefits include controlled release, protection of the active pharmaceutical ingredient and drug targeting. Nanoparticles are expected to offer new solutions e.g. for gene therapy and delivery of peptide drugs. Generally, nanoparticles are applied as an injectable or oral solution, but their use as dried material in formulations such as tablets or inhalable powders is equally conceivable.

The application of nanotechnology to drug delivery is widely expected to create novel therapeutics, capable of changing the landscape of pharmaceutical and biotechnology industries. Various nanotechnology platforms are being investigated, either in development or in clinical stages, and many areas of interest where there will be effective and safer targeted therapeutics for a myriad of clinical applications. It will be evolving out very soon for the benefit of humanity at large. Biodegradable and biocompatible materials for pharmaceutical dosage forms have enabled the advancement of pharmaceuticals by providing better therapy and disease state management for patients through controlled release.

Controlled release delivery is available for many routes of administration and offers many advantages over immediate release delivery. These advantages include reduced dosing frequency, better therapeutic control, fewer side effects, and, consequently, these dosage forms are well accepted by patients. Advancements in polymer material science, particle engineering design, manufacture, and nanotechnology have led the way to the introduction of several marketed controlled release products containing polypeptide drugs and protein drugs that retain their therapeutic activity over pharmaceutical timescales following encapsulation in biodegradable materials.

REFERENCES:

1. Mohanty S, Boga P: Role of Nanoparticles in Drug Delivery System. International Journal of Research in Pharmaceutical and Biomedical Sciences 2010; 1 (2): 41-66.
2. Heidi M.*, MinJi S, Abeer A, Patrick P: Materials for Pharmaceutical Dosage Forms: Molecular Pharmaceutics and Controlled Release Drug Delivery Aspects. Int. J. Mol. Sci. 2010; 11: 3298-3322.
3. Minko T, Sinko P: Drug Delivery Systems-Controlled Drug Release. In Martins Physical Pharmacy and Pharmaceutical Sciences, Ed.; Lippincott Williams & Wilkins: Baltimore, MD, USA 2006: 667–672.
4. Ali N, Shaista R, Patel p, Kofi A: The Role of Oral Controlled Release Matrix Tablets in Drug Delivery Systems. BioImpacts 2012; 2(4): 175-187.
5. Kreuter J:" Nanoparticles as drug delivery system," Encyclopedia of nanoscience and nanotechnology, H. S. Nalwa (Editor), American Scientific Publishers, 2004: 161–180.
6. Abhilash M: Potential applications of Nanoparticles. International Journal of Pharma and Bio Sciences 2010; 1, (1): 1-12.
7. Manivannan R, Kugalur G, Recent Advances in Novel Drug Delivery Systems. IJRAP 2010; 1 (2): 316-326.
8. Yie W, Senshang L: Drug Delivery: Controlled Release; Encyclopedia of Pharmaceutical Technology, Taylor & Francis, Third Edition, Volume 1, Edition 1.
9. Debjit B, Gopinath H, Pragati B,Duraivel S, Sampath K: Controlled Release Drug Delivery System. THE PHARMA INNOVATION 2012; 1(10): 24-32.
10. Gemma V, Judit T, Fernando A: Polymers and Drug Delivery Systems. Current Drug Delivery 2012; 9: 1-29.
11. Bankar V, Gaikwad P, Pawar S: Novel Suatained Release Drug Delivery System. IJPRD 2011; 3(12):1-14.
12. Wischke C, Schwendeman S: Principles of encapsulating hydrophobic drugs in PLA/PLGA microparticles. Int. J. Pharm. 2008; 364: 298–327.
13. Ratnaparkhi M, Gupta J: Sustained Release Oral Drug Delivery System - An Overview. International Journal of Pharma Research & Review 2013; 2(3):11-21.
14. Peng H, Xiao Y, Mao X, Chen L, Crawford R, Whittaker A: Amphiphilic triblock copolymers of methoxy-poly(ethylene glycol)-b-poly(L-lactide)-b-poly(L-lysine) for enhancement of osteoblast attachment and growth. Biomacromolecules 2009; 10: 95–104.

15. Na D, DeLuca P: PEGylation of octreotide: I. Separation of positional isomers and stability against acylation by poly (D,L-lactide-co-glycolide). Pharm. Res.2005; 22: 736–742.
16. Na D, Lee J, Jang S, Lee K: Formation of acylated growth hormone-releasing peptide-6 by poly(lactide-co-glycolide) and its biological activity. AAPS Pharm. Sci. Tech.2007; 8: 43.
17. Berkland C, King M, Cox A, Kim K, Pack D: Precise control of PLG microsphere size provides enhanced control of drug release rate, J. Control. Release 2002; 82: 137–147.
18. Quaglia F, Ostacolo L, Nese G, Rosa G, Rotonda M, Palumbo R, Maglio G: Microspheres made of poly (epsilon-caprolactone)-based amphiphilic copolymers: potential in sustained delivery of proteins. Macromol. Biosci. 2005; 5: 945–954.
19. Nagavarma B, Hemant K, Yadav S*, Ayaz A, Vasudha S, Shivakumar G: Different Techniques for Preparation of Polymeric Nanoparticles- A Review. Asian Journal of Pharmaceutical and Clinical Research 2012; 5(3).
20. Kumar P, Ramakrishna S, Saini T, Diwan P: Influence of microencapsulation method and peptide loading on formulation of Poly (lactide-co-glycolide) insulin nanoparticles. Pharmazie 2006; 61: 613–617.
21. Cheng J, Teply A, Jeong Y, Yim H, Sherifi I, Jon S, Farokhzad C, Khademhosseini A, Langer S: Magnetically responsive polymeric microparticles for oral delivery of protein drugs. Pharm. Res.2006; 23: 557–564.
22. Samuli H: Preparation and Characterization of Poly (Lactic Acid) Nanoparticles for Pharmaceutical Use, Dissertationes bioscientiarum molecularium Universitatis Helsingiensis in Viikki 2/2008: 42.
23. Catarina P, Ronald J, Ribeiro J, Francisco V: Nanoencapsulation I. Methods for preparation of drug-loaded polymeric nanoparticles, Nanomedicine: Nanotechnology, Biology, and Medicine 2006; 2: 8– 21.
24. Mohanraj V, Chen Y: Nanoparticles – A Review, Trop J Pharm Res, 2006, 5 (1): 561-573.
25. Mainardes RM, Urban MC, Cinto PO, Khalil NM, Chaud MV, Evangelista RC, Gremiao MP: Colloidal carriers for ophthalmic drug delivery. Curr Drug Targets 2005; 3: 363-371.
26. Jong WH, Borm PJ: Drug delivery and nanoparticles: Applications and hazards. Int J Nanomedicine 2008; 3(2): 133-149.
27. Varde NK, Pack DW: Microspheres for controlled release drug delivery. Expert Opin Biol Ther 2004; 3(1): 35-51.
1. 28. Zhang L, Gu FX, Chan JM, Wang AZ, Langer RS, Farokhzad OC: Nanoparticles in Medicine: Therapeutic Applications and Developments. Clinical Pharmacology & Therapeutics 2008; 83(5): 761-769.

How to cite this article:
Desai D and Shah D: Implication of Nanoparticles for Controlled Drug Delivery System. *Int J Pharm Sci Res* 2013: 4(7); 2478-2488. doi: 10.13040/IJPSR. 0975-8232.4(7).2478-88